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㉖ **Hormone composition and use.**

㉗ This invention is concerned with a contraceptive formulation and a method of contraception which employs a combination of estrogen and progestin and wherein a short period of relatively dominant estrogenic activity alternates with a short period of relatively dominant progestagenic activity. The invention also concerns a hormonal replacement formulation and method for use in menopausal or castrate women which employs a similar combination of estrogen and progestin.

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Description

HORMONE COMPOSITION AND USE

This invention is concerned with a contraceptive formulation and a method of contraception which employs a combination of estrogen and progestin and wherein a short period of relatively dominant estrogenic activity alternates with a short period of relatively dominant progestagenic activity. Also described are formulations which employ similar hormone combinations for hormonal replacement therapy for menopausal or castrate women.

In the luteal phase of the menstrual cycle, serum progesterone levels increase and progesterone mediated secretory changes occur in the uterine endometrium. The presence of progesterone receptors has been shown to be a necessary prerequisite for progesterone action in the endometrium (see Walters, M.R. and Clark, J.H. Relationship between the quantity of progesterone receptors and the antagonism of estrogen-induced uterotrophic response *Endocrinology* 105:382, 1979) and it is well documented that estrogen priming in the follicular phase of the cycle is responsible for the development of both estrogen and progesterone receptors (see Bayard, F., Damilano, S., Robel, P. and Baulien, E.E. Cytoplasmic and nuclear estradiol and progesterone receptors in human endometrium, *J. Clin Endocrinol Metab.* 46:635, 1978). On the other hand, progesterone exerts a negative feedback effect on its own receptor (see Tseng, L. and Gurpide, E. Effects of progestins on estradiol receptor levels in human endometrium, *J. Clin Endocrinol Metab.* 41:402, 1975) and also acts to downregulate endometrial estrogen receptors possibly by induction of an estrogen receptor regulatory factor (see Leavitt, W.W., Okulicz, W.C., McCracken, J.A., Schramm, W.S. and Robidoux, W.F. Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal, *J. Steroid Biochem.* 22:686, 1985).

These physiologic changes can be reproduced pharmacologically as shown by the induction of estrogen and progestin receptors in postmenopausal women by the administration of ethinyl estradiol (see Kreitmann, B., Bugat, R. and Bayard, F. Estrogen and Progestin Regulation of the Progesterone Receptor Concentration in Human Endometrium, *J. Clin Endocrinol Metab.* 49:926, 1979). Neumannova et al (see Short-Term Effects of Tamoxifen, Medroxy-progesterone Acetate, and Their Combination on Receptor Kinetics and 17beta-Hydroxysteroid Dehydrogenase in Human Endometrium, *Obstet. Gynecol.* 66:695, 1985) have also demonstrated that administration of medroxy-progesterone acetate in estrogen-primed women decreases the concentration of endometrial progestin receptors while at the same time increasing the activity of 17beta-hydroxysteroid dehydrogenase, an enzyme which is responsible for metabolism of estradiol to the less potent estrone.

A complex interaction occurs between estrogen and progesterone or progestin in the human endometrium with the progestins acting as anti-estro-

gens. Estrogen and progestin interactions are also dynamic. For example, estrogen administration increased the concentration of both estrogen and progestin receptors to peak levels, 7 times above baseline, within 3 days (see Ekert, R.L. and Katzenellenbogen, B.S. Human Endometrial Cells in Primary Tissue Culture: Modulation of the Progesterone Receptor Level by Natural and Synthetic Estrogens *In Vitro*, *J. Clin Endocrinol Metab.* 52:699, 1981). A three-fold increase in receptor concentrations occurred within one day. Normal physiologic levels of progesterone in the first 3 days of the luteal phase resulted in a rapid and significant decrease in estrogen receptor number (see Kreitmann-Gimbal, B., Bayard, F., Nixon, W.E. and Hodgen, G.D. Patterns of Estrogen and Progesterone Receptors in Monkey Endometrium During the Normal Menstrual Cycle, *Steroids* 35:471, 1980). Exogenous administration of progesterone to cynomolgous macaques significantly suppressed estrogen receptors within 1 to 2 days (see West, N.B. and Brenner, R.M. Progesterone-Mediated Suppression of Estradiol Receptors in Cynomolgous Macaque Cervix, Endometrium and Oviduct During Sequential Estradiol-Progesterone Treatment, *J. Steroid Biochem.* 22:29, 1985) and medroxy-progesterone acetate was able to significantly suppress progestin receptor levels in premenopausal women within 4 hours (see Neumannova M., Kauppila, A., Kivinen, S. and Vihko, R. Short-Term Effects of Tamoxifen, Medroxy-progesterone Acetate, and Their Combination on Receptor Kinetics and 17beta-Hydroxysteroid Dehydrogenase in Human Endometrium, *Obstet. Gynecol.* 66:695, 1985). In contrast, progesterone withdrawal in the presence of constant estrogen levels has been shown to result in rapid (6 to 12 hours) recovery of nuclear estrogen receptors in sheep endometrium, associated with an estrogen induced biological response, i.e. production of oxytocin receptors (see Leavitt, W.W., Okulicz, W.C., McCracken, J.A., Schramm, W.S. and Robidoux, W.F. Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal, *J. Steroid Biochem.* 22:686, 1985). A similar phenomenon occurs in pregnant guinea pigs when estrogen levels rise relative to progesterone levels prior to parturition (see Alexandrova, M. and Soloff, M.S. Oxytocin receptors and parturition in the guinea pig, *Biol. Reprod.* 22:1106, 1980).

Therefore, it appears that estrogen acts to stimulate both estrogen and progestin receptor concentrations and to induce sensitivity of the endometrium to both estrogen and progestin. Progesterone or progestin exerts an anti-estrogen action by decreasing estrogen receptors and by increasing 17beta-hydroxysteroid dehydrogenase activity in endometrial tissue. However, it appears that the stimulatory effects of progesterone on human endometrial function are of short duration probably because of a self-provoked downregula-

tion of progestin receptors and estrogen receptors. For example, the effect of progesterone on 17 β -hydroxysteroid dehydrogenase peaks at 3 days and is then followed in 2 to 3 weeks by suppression of the enzyme (see Whitehead, M.I., Townsend, P.T., Pryce-Davies, J. et al. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium, *N. Engl. J. Med* 305:1599, 1981).

Currently on the market there are a number of contraceptive formulations which can be classified readily into several general types. The first of these are known as monophasic formulations. These contain a constant amount of estrogen and progestin. Nuisance side effects with these pills depend on the balance between the estrogen and progestin component of the pill. For example, with a relatively dominant progestin pill, the formulation will, over time, result in a depletion of both estrogen and progestin receptors. The result which might be expected is an understimulated or atrophic endometrium which may eventually cause either on-pill amenorrhea or breakthrough bleeding or spotting due to poor epithelialization. On the other hand, with a relatively dominant estrogenic preparation, it is possible that prolonged use could result in endometrial growth with the development of unsupported fragile stroma and subsequent spotting or breakthrough bleeding.

Newer formulations known as triphasics have varying levels of estrogen and progestin; in most cases consisting of relatively constant levels of estrogen with a step-wise increase in progestin throughout the cycle. This pattern of estrogen and progestin administration results in a relatively dominant estrogenic formulation at the beginning of the package with increasing progestagenic activity toward the end of the package. Endometrial stability may be better with these pills since the estrogenic activity at the beginning of the package induces both estrogen and progestin receptors making the endometrium sensitive to the increased levels of progestin towards the end of the package. The progestin activity produces denser, more stable endometrial stroma although the relatively long duration of progestin exposure, toward the end of the package, may still lead to decreased estrogen and progestin receptors and activity. A significant problem with this type of formulation is the low dose of steroids at the beginning of the package which makes these pills vulnerable to drug interactions or missed pills which may lead to breakthrough ovulation. The beginning of the package is the critical time in terms of breakthrough ovulation since the user has just completed a 7 day drug-free interval during which follicular development may begin. Even if pregnancy does not occur, breakthrough ovulation can lead to poor cycle control.

Estrogen replacement therapy is warranted in menopausal women for several reasons. Estrogen replacement will relieve hot flushes and this relief of flushes and night sweats improves sleep patterns and contributes to the patient's general feeling of well-being (see Campbell S., Whitehead M.I. Estrogen therapy and the menopausal syndrome. In

Clinics in Obstetrics and Gynecology: Volume 4. The Menopause. Edited by R.B. Greenblatt, J.W.W. Studd, London, W.B. Saunders, 1977, pages 31-47; Erlik Y., Tataryn I.V., Meldrum D.R. et al. Association of waking episodes with menopausal hot flushes. *JAMA* 24:1741, 1981). Estrogen replacement protects against postmenopausal loss of calcium from the skeleton, especially from vertebral bodies, preventing crush fractures and loss of body height (see Lindsay R., Hart D.M., Forrest, C. et al. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 2:1151, 1980). Several studies have now reported that long-term estrogen therapy is also associated with a reduction in the incidence of classical osteoporotic fractures of the forearm and hip (see Hutchinson, T.A., Polansky, S.M., Fineststein, A. Postmenopausal estrogens protect against fractures of hip and distal radius. *Lancet* 2:706, 1979; Paganini-Hill, A., Ross, R.K., Gerkins, V.R., et al. A case control study of menopausal estrogen therapy in hip fractures. *Annals of Internal Medicine* 95:28, 1981; Weiss N.S., Ure C.L., Ballard J.H. et al. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. *New England Journal of Medicine* 303:1195, 1980). Another beneficial effect of long-term estrogen use is the reduction of the risk of death from Ischemic heart disease probably mediated by changes in blood lipoprotein concentrations (see Ross R.K., Paganini-Hill A., Mack T.M. et al. Menopausal estrogen therapy and protection from ischemic heart disease. *Lancet* 1:858, 1981). Estrogen replacement has also been shown to improve the vascularity and health of the vaginal mucosa and urinary tract. The only major risk factor associated with estrogen administration in the doses required to relieve menopausal symptoms, is hyperstimulation of the endometrium and an increased risk of endometrial cancer (see Cramer D.W., Knapp R.C. Review of epidemiologic studies of endometrial cancer and exogenous estrogen. *Obstetrics and Gynecology* 54:521, 1979; Shapiro S., Coughman D.W., Sloan D., et al. Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. *New England Journal of Medicine* 303:485, 1980).

Estrogens predispose to cancer of the endometrium by stimulating cell mitosis and proliferation and increasing the levels of DNA synthesis and nuclear estradiol receptors in the endometrium (see Whitehead M.I., Townsend P.T., Pryce-Davies J., et al. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New England Journal of Medicine* 305:599, 1981; Whitehead M.I., Townsend P.T., Pryce-Davies J., et al. Actions of progestins on the morphology and biochemistry of the endometrium of postmenopausal women receiving low dose estrogen therapy. *American Journal of Obstetrics and Gynecology*, 142:791, 1982).

The addition of a progestin for 13 days each month has been demonstrated to protect the endometrium from these stimulatory effects of estrogen (see Gambrill R.D., Jr., Massey F.M., Castaneda et al. Use of the progestogen challenge test to reduce the risk

of endometrial cancer. *Obstetrics and Gynecology* 55:732, 1980; Studd J.W.W., Thom M.H., Patterson M.E.L., Wade-Evans T. The prevention and treatment of endometrial pathology in postmenopausal women receiving exogenous estrogens. In: Pasetto N., Paoletti R., Armbus J.L., Editors. *The menopause and postmenopause*. Lancaster MPT Press, 127, 1980).

The addition of a progestin protects the endometrium by reducing nuclear estradiol receptor concentration and thereby decrease nuclear estrogen bioavailability resulting in an antimitotic effect and lowering DNA synthesis. Progestins also increase the activity of endometrial estradiol-17 β -dehydrogenase, an enzyme which metabolize estradiol to estrone, a less potent estrogen (see Whitehead M.I., Townsen P.T., Pryce-Davies J. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New England Journal of Medicine*. 305:1599, 1981; King R.J.B., Townsen P.T., Sittle N.C., et al. Regulation of estrogen and progesterone receptor levels in epithelium and stroma from pre and postmenopausal endometria. *Journal of Steroids and Biochemistry*, 16:21, 1982; Gurpide E. Enzymatic modulation of hormonal action at the target tissue. *Journal of Toxicology and Environmental Health*, 4:249, 1978). The addition of progestin to estrogen replacement therapy may also result in an increase in bone mass when started within 3 years of the menopause (see Nachtigall L.E., Nachtigall R.H., Nachtigall R.D., et al. Estrogen replacement therapy: A 10 year prospective study in relationship to osteoporosis. *Obstetrics and Gynecology* 53:277, 1979; Lindsay R., Hart D.M., Forrest C., et al. Prevention of spinal osteoporosis in oophorectomized women. *Lancet* 2:1151, 1980). However, concerns have been expressed about the potential adverse effects of progestin in suppressing high density lipoprotein cholesterol concentrations (see Hirvonen E., Malkonen M., Manninen V. Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *New England Journal of Medicine* 304:560, 1981). This cholesterol fraction appears to have a protective effect against ischemic heart disease and atherosclerosis. The lowering of HDL cholesterol by progestin could negate the long-term beneficial effects of estrogen in reducing the incidence of myocardial infarction. Other side effects of progestins include acne, breast tenderness, depression and irritability (see Barranco V.P. Effect of androgen dominant and estrogen dominant oral contraceptives on acne. *Cutis* 14:384, 1974; Royal College of General Practitioners. *Oral Contraceptives and Health: An Interim Report*. New York: Pitman, 1974). Since the side effects of progestins appear to be dose dependent, the dose of progestin used with postmenopausal estrogen replacement should be the minimum necessary to achieve endometrial protection. (see Padwick M.L., Pryce-Davies J., Whitehead M.I. A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. *New England Journal of Medicine* 315:930, 1986).

The biological effects of both estrogen and progestin in target tissues such as the endometrium

are dependent on the levels of estrogen and progestin receptors. Both estrogen and progestins exert a modulating influence on the levels of their own receptors. For example, in the luteal phase of the menstrual cycle, serum progesterone levels increase and progesterone mediated secretory changes occur in the uterine endometrium. The presence of progesterone receptors has been shown to be a necessary prerequisite for progesterone action in the endometrium (see Walters M.R. and Clark J.H. Relationship between the quantity of progesterone receptors and the antagonism of estrogen-induced uterotrophic response. *Endocrinology* 105:382, 1979) and it is well documented that estrogen priming in the follicular phase of the cycle is responsible for the development of both estrogen and progesterone receptors (see Bayard F., Damilano S., Robel P. and Baulieu E.E. Cytoplasmic and nuclear estradiol and progesterone receptors in human endometrium. *Journal Clinical Endocrinology and Metabolism* 46:635, 1978). On the other hand, progesterone exerts a negative feedback effect on its own receptor (see Tseng L. and Gurpide E. Effects of progestins on estradiol receptor levels in human endometrium. *Journal Clinical Endocrinology and Metabolism* 41:402, 1975) and also acts to downregulate endometrial estrogen receptors possibly by induction of an estrogen receptor regulatory factor (see Leavitt W.W., Okulicz W.C., McCracken J.A., Schramm W.S. and Robidoux W.F., Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal. *Journal Steroid Biochemistry* 22:686, 1985).

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A complex interaction occurs between estrogen and progesterone or progestin in the human endometrium with the progestins acting as anti-estrogens. Estrogen and progestin interactions are also dynamic. For example, estrogen administration increased the concentration of both estrogen and progestin receptors to peak levels, 7 times above baseline, within 3 days (see Ekert R.L. and Katzenellenbogen B.S. Human endometrial cells in primary tissue culture: Modulation of the progesterone receptor level by natural and synthetic estrogens in

vitro. *Journal Clinical Endocrinology and Metabolism* 52:699, 1981). A three-fold increase in receptor concentrations occurred within one day. Normal physiologic levels of progesterone in the first 3 days of the luteal phase resulted in a rapid and significant decrease in estrogen receptor number (see Kreitmann-Gimbal B., Bayard F., Nixon W.E. and Hodgen G.D. Patterns of estrogen and progesterone receptors in monkey endometrium during the normal menstrual cycle. *Steroids* 35:471, 1980). Exogenous administration of progesterone to cynomolgous macaques significantly suppressed estrogen receptors within 1 to 2 days (see West N.B. and Brenner R.M. Progesterone-mediated suppression of estradiol receptors in cynomolgous macaque cervix, endometrium and oviduct during sequential estradiol-progesterone treatment. *Journal Steroid Biochemistry* 22:29, 1985) and medroxyprogesterone acetate was able to significantly suppress progesterin receptor levels in premenopausal women within 4 hours (see Neumannova M., Kauppila A., Kivinen S. and Vihko R. Short-term effects of tamoxifen, medroxyprogesterone acetate, and their combination on receptor kinetics and 17beta-hydroxysteroid dehydrogenase in human endometrium, *Obstetrics and Gynecology* 66:695, 1985). In contrast, progesterone withdrawal in the presence of constant estrogen levels has been shown to result in rapid (6 to 12 hours) recovery of nuclear estrogen receptors in sheep endometrium, associated with an estrogen induced biological response, i.e. production of oxytocin receptors (see Leavitt W.W., Okulicz W.C., McCracken J.A., Schramm W.S. and Robidoux W.F., Jr. Rapid recovery of nuclear estrogen receptor and oxytocin receptor in the ovine uterus following progesterone withdrawal. *Journal Steroids and Biochemistry* 22:686, 1985). A similar phenomenon occurs in pregnant guinea pigs when estrogen levels rise relative to progesterone levels prior to parturition (*Biology and Reproduction* 22:1106, 1980).

Therefore, it appears that estrogen acts to stimulate both estrogen and progesterin receptor concentrations and to induce sensitivity of the endometrium to both estrogen and progesterin. Progesterone or progesterin exerts an anti-estrogen action by decreasing the concentration of estrogen receptors and by increasing 17beta-hydroxysteroid dehydrogenase activity in endometrial tissue. However, it appears that the stimulatory effects of progesterone on human endometrial function are of short duration probably because of a self-provoked downregulation of progesterin receptors (see Neumannova M., Kauppila A., Kivinen S. and Vihko R. Short-term effects of tamoxifen, medroxyprogesterone acetate, and their combination on receptor kinetics and 17beta-hydroxysteroid dehydrogenase in human endometrium, *Obstetrics and Gynecology* 66:695, 1985; Whitehead M.I., Townsen P.T., Pryce-Davies J. et al. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New England Journal of Medicine*. 305:1599, 1981). For example, the effect of progesterone on 17beta-hydroxysteroid dehydrogenase peaks at 3 days and is then followed in 2 to 3 weeks by suppression of the enzyme (see White-

head M.I., Townsend P.T., Pryce-Davies J. et al. Effects of estrogens and progestins on the biochemistry and morphology of the postmenopausal endometrium. *New England Journal of Medicine* 305:1599, 1981).

Current hormonal replacement consists of continuous (daily or cyclic) (example day 1-25 of each month) estrogen administration with the addition of a progestin for 10-13 days (example days 13-25) each month. This type of replacement regimen is effective in preventing menopausal symptoms and at the same time, protects the endometrium against the development of hyperplasia or adenocarcinoma. However, the cyclic administration of a progestin leads to a scheduled withdrawal bleed or period in 65-75% of women (see Hellberg D., Nilsson S. Comparison of a triphasic estradiol/norethisterone acetate preparation with and without estriol component in the treatment of climacteric complaints; *Maturitas* 5:233, 1984; Christensen M.S., Hagen C., Christiansen C., Transbol I. Dose response evaluation of cyclic estrogen/gestagen in postmenopausal women: Placebo controlled trial of its gynecologic and metabolic actions. *American Journal of Obstetrics and Gynecology*. 144:873, 1982). This withdrawal bleeding is usually not welcomed by the patient and can lead to problems with compliance. Also because the progestin administration is preceded by up to 13-16 days of unopposed estrogen therapy with endometrial proliferation and estrogen and progesterin receptor induction, it is possible that a high dose of progestin is required to antagonize these effects resulting in a greater chance of side effects and adverse metabolic effects. Newer continuous low dose estrogen and progesterin regimens for hormonal replacement may avoid the problem of withdrawal bleeding (see Magos A.L., Brincatt M., O'Dowd T., et al. Amenorrhea and endometrial atrophy following continuous oral estrogen and progestogen therapy in postmenopausal women. *Maturitas* 6:145, 1984). However, daily administration of a progestin in these regimens induces depletion of both estrogen and progesterin receptors resulting in endometrial atrophy which may be associated with breakthrough bleeding. Since abnormal bleeding in a postmenopausal woman is known to be associated with endometrial carcinoma, it must be investigated by endometrial sampling for hypertrophy usually by D&C. Daily administration of a progestin also raises the concern that the favourable effects of estrogen on HDL cholesterol metabolism will be adversely affected with a fall in HDL cholesterol (see Notelovitz M., Gudat J.C., Ware M.D., Dougherty M.C. *British Journal of Obstetrics and Gynecology*. 90:171, 1983).

The present invention provides a product containing estrogen and progestin as a combined preparation for administering a plurality of unit dosages of a relatively dominant estrogen activity combination and for administering a plurality of unit dosages of a relatively dominant progestin activity combination. In general, in the product the unit dosages are arranged for the administration alternately of a number of unit dosages of the relatively dominant

estrogen activity combination and of a number of unit dosages of the relatively dominant progestin activity combination, each said number of unit dosages preferably consisting of 1 to 5 unit dosages, more preferably 2 to 4 and most preferably 3 unit dosages, the product preferably being presented in the form of packages each containing 20 to 35 unit dosages.

In one aspect the product is for administration to females of child bearing age as a contraceptive and in another aspect is for hormone replacement therapy for administration to a female in need of such treatment, preferably wherein the female is of child bearing age or older in whom ovarian estrogen and progesterone production has been interrupted either because of natural menopause, surgical, radiation or chemical ovarian oviation of extirpation or premature ovarian failure.

The invention also provides the new use of estrogen and progestin in the manufacture of the new product. The invention also provides new methods of treatment comprising administering two types of hormone-containing dosage combinations.

The present invention provides a pharmaceutical preparation for administration to a female of child bearing age for contraceptive purposes, which comprises a total of twenty to thirty-five unit dosages, each unit dosage for consecutive daily administration; each unit dosage comprising a combination of estrogen and progestin selected from a relatively dominant estrogen activity combination and a relatively dominant progestin activity combination, with a plurality of dominant estrogen activity dosages being alternated with a plurality of dominant progestin dosages; and each unit dosage also comprising a pharmaceutically acceptable inert carrier when required.

In another aspect, the invention provides a method of contraception which comprises administering to a female of child bearing age, in daily sequence, twenty to thirty-five unit dosages; each unit dosage comprising a combination of estrogen and progestin and being selected from a relatively dominant estrogen activity combination and a relatively dominant progestin activity combination, a plurality of dominant estrogen activity unit dosages being alternated with a plurality of dominant progestin activity unit dosages.

In a preferred form of the invention, dominant estrogen activity dosages are used to begin and end the twenty to thirty-five unit dosages.

Preferred methods of contraception involve twenty-one and twenty-four unit dosages.

In another aspect of the invention, there may be included an additional seven or four unit dosages in the pharmaceutical preparation which may comprise a placebo or any other hormone-free agent. These are usually taken at the completion of the twenty-one or twenty-four unit dosages.

Thus, in the present disclosure, a formulation is described that is better able to protect the endometrium against the estrogen related risk of endometrial hyperplasia and adenocarcinoma with a lower dose of progestin by administering progestin for a short period of time alternating with a short period of

absent or reduced progestin. It has been demonstrated that a protective effect of progestin is related to the duration of administration with 12-13 days per month appearing to be the minimum required for greatest protection. The present formulation administers a low dose of progestin intermittently throughout the month for a minimum of 15 days exposure.

The present invention provides a pharmaceutical preparation for administration to a female of child bearing age or older in whom ovarian estrogen and progesterone production has been interrupted either because of natural menopause, surgical, radiation, or chemical ovarian ablation or extirpation or premature ovarian failure, which comprises a plurality of unit dosages, each unit dosage for continuous consecutive daily administration and comprising combinations of estrogen and progestin selected from a combination with relatively dominant estrogen activity and a combination with relatively dominant progestin activity, with a plurality of dominant estrogen dosages being alternated with plurality of dominant progestin dosages, and each unit dosage also comprising a pharmaceutically acceptable inert carrier when required.

In another aspect, the invention provides a method of hormonal replacement therapy for administration to a female in need of such treatment, in particular to a female of child bearing age or older to whom ovarian estrogen and progesterone production has been interrupted either because of natural menopause, surgical, radiation, or chemical ovarian ablation or extirpation or premature ovarian failure, which comprises administering continuously and consecutively, in daily sequence, a plurality of daily unit dosages comprising combinations of estrogen and progestin, selected from a combination with relatively dominant estrogen activity and a combination with relatively dominant progestin activity, a plurality of the dominant estrogen activity unit dosages being alternated with a plurality of the dominant progestin activity unit dosages.

The contraceptive formulation of the present invention results in better cycle control. Intermittent increases in estrogen activity stimulate endometrial growth and progestin receptors. This makes the endometrium more sensitive to subsequent progestin activity which limits growth by decreasing estrogen receptors and increasing 17beta-hydroxysteroid dehydrogenase. Interaction of progestin with progestin receptors induces secretory changes in the endometrium which results in a denser stroma and endometrial stability. A return to relatively dominant estrogenic activity then again stimulates estrogen and progestin receptors and renews endometrial sensitivity to progestin. This push/pull activity keeps endometrial activity within a narrow range depending on the number of days of estrogenic and progestagenic activity.

The design of the present contraceptive invention avoids low levels of steroids present during the first part of the triphasic package which makes the triphasic formulations more sensitive to drug interactions and missed pills. As a result, less pill failures in terms of pregnancy occur and also cycle control is

better because of fewer breakthrough ovulations.

The current contraceptive formulation allows better progestational effect with less progestin. With the current formulation the dose of progestin is significantly decreased compared to most monophasic preparations and a total steroid dosage is achieved which is lower than that of the present triphasics and yet the present formulation offers better cycle control and efficacy. A reduction in progestin dosage results in less negative impact on HDL cholesterol levels. HDL cholesterol has been shown to be protective against development of atherosclerosis and its concentration is increased by estrogen and decreased by progestin.

Alternatively, the reduction in progestin dose possible with the subject contraceptive formulation results in a pill that also has good estrogenic effect. Therefore, this formulation is a good one for the management of acne, oily skin and hirsutism and also has less chance of on-pill amenorrhea.

It is thought that the current contraceptive formulation is better able to inhibit ovulation with lower doses of steroids, since it has been demonstrated that estrogen priming increases progesterone receptor concentration in the hypothalamus and anterior pituitary gland in a number of animal species (see Katzenellenbogen, B.S. Dynamics of steroid hormone receptor action, Annual Rev. Physiol. 42:17, 1980). Therefore, by allowing intermittent estrogenic priming to occur by administering the preparation of estrogen and progestin in the alternating fashion of the present method, it is possible to potentiate the central negative feedback actions of both progestin and estrogen.

The hormonal replacement formulation of the present invention results in the absence of withdrawal bleeding; intermittent increases in estrogen activity; and stimulation of endometrial growth and progestin receptors. This makes the endometrium more sensitive to subsequent progestin activity which limits growth by decreasing estrogen receptors and increasing 17beta-hydroxysteroid dehydrogenase. Interaction of progestin with progestin receptors induces secretory changes in the endometrium which results in a denser stroma and endometrial stability. A return to relatively dominant estrogenic activity then again stimulates estrogen and progestin receptors and renews endometrial sensitivity to progestin. This push/pull activity keeps endometrial activity within a narrow range depending on the number of days of estrogenic and progestagenic activity and maintains a stable endometrium resulting in the absence of breakthrough or withdrawal bleeding.

This hormonal replacement formulation allows better progestational effects with less progestin. With the current formulation the dose of progestin is significantly decreased compared with a preparation containing constant daily administration of a progestin. A total steroid dosage is achieved which is similar to or even lower than that of the present cyclic method of administering estrogen and progestin for hormonal replacement therapy of ovarian failure. A reduction in progestin dosage results in less negative impact on HDL cholesterol levels. HDL

cholesterol has been shown to be protective against the development of atherosclerosis. The concentration of HDL cholesterol is increased by estrogen and decreased by progestin.

The estrogens which may be employed as a component in the regimens of this invention may be any of those conventionally available. Typically, the estrogen may be selected from the group comprising synthetic and natural estrogens. The synthetic estrogens may be selected from, for example, ethinyl estradiol, mestranol and quinestranol. Particularly of interest are 17alpha-ethinylestradiol and esters and ethers thereof. The preferred estrogen is 17alpha-ethinylestradiol. The natural estrogens may include, for example, conjugated equine estrogens, estradiol-17beta, estradiol valerate, estrone, piperazine estrone sulphate, estriol, estriol succinate, desogestrel and polyestrol phosphate.

The progestin component may be any progestationally active compound. Thus, the progestin may be selected from progesterone and its derivatives such as, for example, 17-hydroxy progesterone esters, 19-nor-17-hydroxy progesterone esters, 17alpha-ethinyltestosterone and derivatives thereof, 17alpha-ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxy-progesterone acetate, norethynodrel, allylestrenol, lynoestrenol, fulgestanol acetate, medrogestone, norgestrienone, dimethiderone, ethisterone, cyproterone, lavo-norgestrel, d-norgestrel, d-17alpha-acetoxy-13beta-ethyl-17alpha-ethinyl-gon-4-en-3-one oxime, cyproterone acetate, gestodene and norgestimate. Preferred progestins are norethindrone, d-norgestrel and norgestimate.

In a preferred form of the invention, the plurality of dosages may comprise from one to five unit dosages, but preferably three unit dosages are employed. Thus, in a preferred form of the invention, three unit dosages of relatively dominant estrogen activity are alternated with three unit dosages of relatively dominant progestin activity and so on for a total of twenty-one or twenty-four unit dosages. Four or seven unit dosages which are free of hormone are included to approximate the natural twenty-eight day menstrual cycle of the female. These pills may comprise a placebo or any other hormone-free agent. Examples of suitable alternative agents include vitamins, such as iron supplements. Where the total unit dosages do not comprise multiples of three, an appropriate number of hormone-free unit dosages may be included to make up the total required units.

Generally, the quantities of estrogen and progestin incorporated in the formulation of the invention are dependent on the type of estrogen or progestin selected. However, the quantities employed are generally less than those used in the currently marketed formulations for reasons mentioned earlier. In the present formulation, the estrogen level is kept constant, while the progestin level is adjusted up or down to produce the required estrogen or progestin dominance. The selection of quantity is dependent on the type of estrogen or progestin since each hormone has its own specific activity.

Typically for the contraceptive formulation, the amount of estrogen per unit dose may range from a minimum of about 0.020 mg. to a maximum of about 0.050 mg. of 17alpha-ethinylestradiol or its equivalent dosage in other synthetic or natural estrogens and the amount of progestin per unit dosage may range from a minimum of about 0.00 mg. of norethindrone or its equivalent in a synthetic or natural progestin to a maximum of about 1.00 mg. Thus, the maximum amount of hormone over the 21 days of administration may range from about 6.72 mg. to about 22.05 mg. (These amounts generally refer to oral dosages.)

Some preferred combinations include the following:

1. Three unit dosages of 0.035 mg. of 17alpha-ethinyl-estradiol with 0.5 mg. of norethindrone, alternating with three unit dosages of 0.035 mg. of 17alpha-ethinylestradiol with 0.75 mg. of norethindrone for a total of 7 groups of three, beginning and ending with the 0.5 mg. of norethindrone combination.

2. Three unit dosages of 0.035 mg. of 17alpha-ethinyl-estradiol and 0.5 mg. of norethindrone alternating with three unit dosages of 0.035 mg. of 17alpha-ethinyl-estradiol and 0.35 mg. of norethindrone, beginning and ending with the 0.5 mg. of norethindrone combination.

Typically in the hormone replacement formulations, the amount of estrogen per unit dose may range from a minimum of about 0.3 mg of estrone sulphate or its equivalent to a maximum of about 2.5 mg of estrone sulphate or its equivalent. The amount of progestin per unit dosage may range from a minimum of 0 mg to a maximum of about 5 mg of norethindrone or its equivalent. (These amounts generally refer to oral dosages.)

Some preferred combinations include the following:

1. Three units dosages of 0.75 mg piperazine estrone sulphate alternating with three unit dosages of 0.75 mg of piperazine estrone sulphate with 0.35 mg of norethindrone.

2. Three unit dosages of 0.75 mg piperazine estrone sulphate and 0.15 of norethindrone alternating with three unit dosages of 0.75 mg of piperazine estrone sulphate and 0.35 mg of norethindrone.

The above combinations may also be grouped into three's and four's, starting with either three or four day groups and ending with the other. For the normal replacement therapy it may be advantageous for the groups of dominant estrogen activity combination to comprise one more unit dosage than the dominant progestin activity combination unit dosages, or vice versa, for instance the numbers in the groups being 2 and 3 or 3 and 4.

The formulations of the invention may be administered orally, preferably in tablet form, parenterally, sublingually, transdermally, intravaginally, intranasally or buccally. The method of administration determines the types of estrogens and progestins useful in the formulation, as well as the amounts per unit dosage.

Methods for transdermal administration including

the associated methods for manufacturing such systems are well known in the art. In this connection, reference may be had to U.S. Patents Nos. 4,752,478, 4,685,911, 4,438,139 and 4,291,014.

Generally speaking, the formulations are prepared according to conventionally known procedures in accordance

with the method of administration. Thus, the active ingredients are prepared according to known methods in a pharmaceutically acceptable form for administration. These ingredients, in their required quantities are combined with the appropriate pharmaceutical carriers such as additives, vehicles and/or flavour ameliorating substances. These substances may be referred to as diluents, binders and lubricants. Gums, starches and sugars are also common terms. Typical of these types of substances or excipients are pharmaceutical grades of mannitol, lactose starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate and the like. The active ingredient(s) may comprise from about 0.01% by weight to about 99.99% by weight of the total formulation and the remainder comprises the pharmaceutically acceptable carrier. The percentage of active ingredient(s) may vary according to the delivery system or method of administration and is chosen in accordance with conventional methods known in the art.

Thus, the active ingredients are compounded with the chosen carrier and in for example the case of a tablet form, placed in a tablet molding apparatus to form the tablets which are subsequently packaged in accordance with the chosen regimen.

In the oral form of the formulation, the contraceptives are preferably produced in the form of a pharmaceutical kit or package, with the daily dosages arranged for proper sequential administration. Thus, in another aspect, the present invention also provides a pharmaceutical package which contains combination-type contraceptives in multiple dosage units in a synchronized, fixed sequence, wherein the sequence or arrangement of the dosage units corresponds to the stages of daily administration. This can be known as a multi-preparation pack.

Preferably, such packages are in the form of a transparent package with twenty-eight dosage units arranged sequentially and consisting of twenty-one or twenty-four tablets containing the combined estrogen/progestin formulation set up for the cyclical regimen of the invention and seven or four placebos thereafter.

Preferably the placebo tablets and tablets containing the hormones are different colours or shapes. Data indications may be provided on the packaging. The packaging may be a tube or box or a strip. The box may be circular, square, or otherwise shaped with the tablets being accommodated separately therein for ease of administration. Date indications may appear adjacent each tablet corresponding with the days on which each tablet is to be taken. Some indication of the sequence in which the tablets are to be taken preferably appears on the packaging regardless of its form.

In the following examples, specific embodiments

of the present invention are set forth. These are meant to be illustrative of the invention and are not meant to limit it in any way. All parts and percentages are by weight, unless indicated otherwise.

EXAMPLE 1

1

Three-day phases of unit dosages of 17alpha-ethinyl-estradiol(EE) 0.035 mg. and norethindrone (NET) 0.5 mg. alternating with three-day phases of unit dosages of EE 0.035 mg. and NET 0.75 mg. for a total of 7 phases (21 days or 21 unit dosages) beginning and ending with the NET 0.5 mg. combination.

EXAMPLE 2

Three-day phases (unit dosages of EE 0.035 mg. and NET 0.5 mg.) alternating with three-day phases of EE 0.035 mg. and NET 0.35 mg., beginning and ending with the 0.5 mg. combination

EXAMPLE 3

Two-day phases of unit dosages of EE 0.035 mg alternating with unit dosages of EE 0.035 mg and NET 0.35 mg, beginning and ending with the first unit dosage and running for 24 days total.

EXAMPLE 4

Three-day phases of unit dosages of EE 0.035 mg and NET 0.15 mg alternating with EE 0.035 mg and NET 0.35 mg and running for 24 days total.

EXAMPLE 5

Three-day and four-day phases of each of the above combinations as set forth in Examples 1 and 2, starting with either 3 or 4-day phases and ending with the other.

EXAMPLE 6

Four-day and three-day phases of each of the above are prepared, starting with a four-day unit dosage of 0.5 mg. NET and 0.035 mg. EE and ending with 0.75 mg. NET and 0.035 mg. EE.

EXAMPLE 7

Three-day and four-day phases of each of the

above formulations starting with a three-day phase of 0.35 mg. NET with 0.035 mg. EE and ending with a four-day phase of 0.5 mg. NET and 0.035 mg. EE.

EXAMPLE 8

One-day alternating phases using the unit dosages set forth in Examples 1 and 2.

EXAMPLE 9

Two-day alternating phases ending or beginning with a single 3-day phase, using the unit dosage formulations set forth in Examples 1 or 2.

EXAMPLE 10

Three-day phases of EE 0.035 mg. and levonorgestrel (D-norgestrel) 0.05 mg. alternating with 3-day phases of EE 0.035 mg. and levonorgestrel 0.075 mg.

EXAMPLE 11

Three-day phases of EE 0.035 mg. and norgestimate 0.05 mg. alternating with EE 0.035 mg. and norgestimate 0.075 mg.

EXAMPLE 12

Three-day phases of EE 0.035 mg. and norgestimate 0.05 mg. alternating with EE 0.035 and norgestimate 0.035 mg.

EXAMPLES 13 & 14

One formulation was administered to 2 women for a total of 3 cycles to establish that cycle control, in terms of breakthrough bleeding, is acceptable. The test formulation consisted of three unit dosages of 0.035 mg. of 17alpha-ethinylestradiol and 0.5 mg. of norethindrone alternating with three unit dosages of 0.035 mg. of 17alpha-ethinylestradiol and 0.75 mg. of norethindrone for a total of 7 groups of three, beginning and ending with the 0.5 mg. of norethindrone combination.

EXAMPLE 13

A 23 year old nulliparous woman who had not taken any hormonal formulation including oral con-

traceptives for three months agreed to take the test formulation of the invention for two cycles. The subject was in good health and did not smoke. The subject had no contraindications to the use of oral contraceptives and her menstrual cycles were regular. The subject started the test formulation on the fifth day of her cycle (onset of menstruation is considered day 1) for 21 consecutive days (first cycle), followed by a 7 day interval which was free of any hormone and then restarted the test formulation for another 21 days (second cycle). In the first cycle the subject had no bleeding or spotting while taking the test formulation and had a withdrawal bleed starting on the second day of the hormone free interval. The withdrawal bleed lasted for 5 days and was lighter than a normal menstrual period consisting of reddish-brown spotting. There was no discomfort associated with the withdrawal bleeding. In the second cycle, the subject was also free of bleeding or spotting while taking the test formulation and again had a brownish, very light withdrawal bleed which began two days after stopping the test formulation and lasted for 6 days. The subject experienced no side effects during the two test cycles.

EXAMPLE 14

The subject was a healthy, 27 year old nulliparous woman who was currently taking a commercially available oral contraceptive formulation containing 17alpha-ethiny-lestradiol and dl-norgestrel (Triphasil (Trade mark of Wyeth Pharmaceuticals)). The subject agreed to take the test formulation of the invention for one cycle. The subject started the test formulation after a 7 day hormone free interval following the last Triphasil tablet. The test formulation was taken for 21 days followed by a 7 day drug free interval. The subject had no spotting or bleeding during the time she took the test formulation and experienced a withdrawal bleed which began two days after stopping the test formulation. The withdrawal bleeding lasted four days, was painless and was the same amount and colour as a normal menstrual period for the subject. The subject had no side effects during the test formulation. Both subjects found the test formulation to be acceptable in terms of cycle control, side effects and menstrual bleeding.

Examples illustrating the Hormone-Replacement Therapy.

EXAMPLE 15

Three-day phases of unit dosages of 0.75 mg piperazine estrone sulphate alternating with three-day phases of unit dosages of estrone sulphate 0.75 mg and NET 0.35 mg given continuously and orally.

EXAMPLE 16

5 Three-day phases (unit dosages of estrone sulphate 0.75 mg and norethindrone 0.15 mg) alternating with three-day phases of estrone sulphate 0.75 mg and norethindrone 0.35 mg given continuously and orally.

EXAMPLE 17

15 Three-day phases of oral micronized 17beta-estradiol 1 mg alternating with three-days of 17beta-estradiol 1 mg and norethindrone .35 mg given continuously.

EXAMPLE 18

25 Three-day phases of transdermal 17beta-estradiol (100 ug/day) alternating with three-days of transdermal 17beta-estradiol (100 ug/day) and transdermal norethindrone (.35 mg/day) given continuously.

EXAMPLE 19

30 Three-day phases of estrone sulphate 1.25 mg alternating with three-day phases of estrone sulphate 1.25 mg and norethindrone 0.35 mg given continuously and orally.

EXAMPLE 20

40 Three-day phases of estrone sulphate 1.25 mg alternating with three-day phases of estrone sulphate 1.25 mg and norethindrone 0.5 mg given continuously and orally.

EXAMPLE 21

50 One-day or two-day alternating phases using the unit dosages set forth in Examples 13 and 14 given continuously and orally.

EXAMPLE 22

60 Three-day phases of estrone sulphate 0.75 mg alternating with three-day phases of estrone sulphate 0.75 mg and norgestimate 0.050 mg given continuously and orally.

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EXAMPLE 23

Three-day and four-day phases of each of the combinations as set forth in Examples 13 and 14, starting with either a 3- or 4-day phase and given continuously and orally.

EXAMPLE 24

Two-day and three-day phases of each of the combinations as set forth in Examples 13 and 14, starting with either a 2- or 3-day phase and given continuously and orally.

While the present invention has been described with reference to specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material or composition of matter, process, process step or steps, or then present objective to the spirit of this invention without departing from its essential teachings.

Claims

1. A product containing estrogen and progestin as a combined preparation for administering a plurality of unit dosages of a relatively dominant estrogen activity combination and for administering a plurality of unit dosages of a relatively dominant progestin activity combination.

2. A product according to claim 1 in which the unit dosages are arranged for the administration alternately of a number of unit dosages of the relatively dominant estrogen activity combination and of a number of unit dosages of the relatively dominant progestin activity combination, each said number of unit dosages preferably consisting of 1 to 5 unit dosages, more preferably 2 to 4 and most preferably 3 unit dosages, the product preferably being presented in the form of packages each containing 20 to 35 unit dosages.

3. A product according to claim 1 or claim 2 which comprises a plurality of hormone-free unit dosages for administration after the hormone-containing unit dosages, the product preferably being presented in the form of packages, each containing 28 unit dosages in total of which suitably 21 or 24 are hormone-containing unit dosages and 7 or 4 are hormone-free unit dosages.

4. A product according to any preceding claim which is for administration to females of child bearing age as a contraceptive.

5. A product according to any of claims 1 to 3 which is for hormone replacement therapy for administration to a female in need of such treatment, preferably wherein the female is of child bearing age or older in whom ovarian estrogen and progesterone production has been interrupted either because of natural menopause, surgical, radiation or chemical ovarian oviation of extirpation or premature ovarian failure.

6. Use of estrogen and progestin in a method of manufacturing a product characterised in that the product is as defined in any preceding claim.

7. Method of treatment of a female which comprises administering consecutively and in daily sequence a plurality of daily unit dosages each unit dosage being selected from a relatively dominant estrogen activity combination and a relatively dominant progestin activity combination characterised in that a number of the dominant estrogen activity combination unit dosages are alternated with a number of the dominant progestin activity unit dosages, preferably starting and more preferably also finishing with a number of dominant estrogen activity combination unit dosages.

8. Method according to claim 7 having the further characteristic features of any of claims 2 to 5.

9. A product according to any of claims 1 to 5, a use according to claim 6 or a method according to claim 7 or claim 8, in which the estrogen is selected from synthetic and natural estrogens, preferably selected from 17alpha-ethinylestradiol and esters and ethers thereof or from natural estrogens selected from conjugated equine estrogens, 17beta-estradiol, estradiol valerate, estrone, estrone sulphate, piperazine estrone sulphate, estriol, estriol succinate and polyestrol phosphate or synthetic estrogens comprising ethinyl estradiol, mestranol and quinestranol.

10. A product according to any of claims 1 to 5 and 9, a use according to claim 6 or 9 or a method according to any of claims 7 to 9 in which the progestin is selected from progesterone, 17-hydroxy progesterone esters, 19-nor-17-hydroxy- progesterone esters, 17alpha-ethinyl-testosterone, 17alpha-ethinyl-19-nor-testosterone and derivatives thereof, norethindrone, norethindrone acetate, ethynodiol diacetate, dydrogesterone, medroxyprogesterone acetate, norethynodrel, allylestrenol, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, dimethisterone, ethisterone, cyproterone, cyproterone acetate, levonorgestrel, d-norgestrel, dl-norgestrel, d-17beta-acetoxy-13beta-ethyl-17alpha-ethinylgon-4-en-3-one oxime, gestodene, norgestimate and desogestrel, and is preferably norethindrone or norgestimate or for a contraceptive product is di-norgestrel or, for a hormonal replacement product, is progesterone

11. A product according to any of claims 1 to

4, 9 and 10, a use according to any of claims 6, 9 and 10 or a method according to any of claims 7 to 10 which is a contraceptive in which the amount of estrogen per unit dosage ranges from a minimum of about 0.020 mg. to a maximum of about 0.050 mg. of 17alpha-ethinylestradiol or its equivalent dosage in another synthetic or natural estrogen and the amount of progestin per unit dosage may range from a minimum of about 0.00 mg, preferably about 0.2 mg, to a maximum of about 1.00mg. of norethindrone or its equivalent in a synthetic or natural progestin.

12. A product, use or method according to claim 11, in which the dominant estrogen combination unit dosages contain 0.035 mg 17alpha-ethinylestradiol and 0.35-0.5 mg norethindrone and the dominant progestin combination unit dosages contain 0.035 mg 17alpha-ethinylestradiol and 0.5-0.75 mg norethindrone, and in which the unit dosages are preferably for administration in alternating groups of three of each type of hormone containing unit dosage.

13. A product according to any of claims 1 to 3, 5, 9 and 10, a use according to any of claims 6, 9 and 10 or a method according to any of claims 7 to 10 which is for hormonal replacement therapy in which the amount of estrogen per unit dosage ranges from a minimum of about

0.3 mg to a maximum of about 5.0 mg preferably to a maximum of about 2.5 mg of piperazine estrone sulphate or its equivalent dosage in another synthetic or natural estrogen and the amount of progestin per unit dosage may range from a minimum of about 0.0 mg to a maximum of about 5.0 mg of norethindrone or its equivalent in a synthetic or natural progestin.

14. A product, use or method according to claim 13 in which the unit dosages are for oral administration and in which the dominant estrogen combination unit dosage containing 0.75 mg piperazine estrone sulphate and 0.015 mg norethindrone and the dominant progestin combination unit dosages contain 0.75 piperazine estrone sulphate and 0.35 mg norethindrone and in which the unit dosages are preferably for administration in alternating groups of three of each type of hormone-containing unit dosage.

15. A product, use or method according to claim 13 in which the unit dosages are for transdermal administration and are for administration in alternating three day periods of 17beta-estradiol at 0.1 mg/day plus norethindrone at 0-0.15 mg/day and three day periods of 17beta-estradiol at 0.1 mg/day plus norethindrone at 0.35 mg/day.

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